

Effects of bisphenol A and its chemical analogues on the microenvironment and female breast cancer development (Review)

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Abstract. Female breast cancer (BC) is the fourth most commonly diagnosed malignancy globally and its incidence is rising. Endocrine-disrupting chemicals can bind to and activate oestrogen receptors, disrupt the microenvironment and promote oncogenic pathways. Consequently, bisphenols have been associated with the potential onset of breast carcinogenesis. The present narrative review discusses bisphenol A (BPA) and three of its chemical analogues, bisphenol AF (BPAF), bisphenol S (BPS) and bisphenol F (BPF), as well as their potential role in altering the breast microenvironment. In doing so, the present review highlights the effects that BPA, and its analogues may have in driving carcinogenesis in the microenvironment through endocrine disruption, epigenetic changes, and the modulation of immune and inflammatory pathways. Further studies are required to better understand these interactions in order to develop preventative strategies

and regulatory policies to mitigate the potential risk of BC development through environmental exposure to BPA, BPAF, BPS and BPF.

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1. Introduction

Breast cancer (BC) is the most prevalent type of cancer among women worldwide, with 2.3 million new cases diagnosed each year (1). The aetiology of BC is multifactorial and involves genetic, hormonal, environmental and lifestyle factors. While the precise mechanisms remain poorly understood, research has identified various risk factors, including non-modifiable factors such as age, genetic predisposition (*BRCA1/2* mutations) and hormone levels. Modifiable factors include lifestyle choices, the use of oral contraceptives or hormone replacement therapy (2) and parity (3). In addition, a high mammographic density has been found to be associated with an increased risk of BC development (4).

At a cellular level, the majority of BC cases originate in the epithelial lining of breast ducts and lobules, termed ductal or lobular carcinoma *in situ*. Once malignant cells spread to nearby structures or tissues, the cancer becomes invasive carcinoma. BC can be classified into four main molecular subtypes based on the hormone receptor (HR; i.e., oestrogen and progesterone) and the human epidermal growth factor receptor 2 (HER2) status and include luminal A (HR⁺ and HER2⁻), luminal B (HR⁺ and HER2⁺), triple-negative (HR⁻ and HER2⁻), and HER2-positive (5). The current standard of care depends on curative intent or palliative approaches, and can include a combination of chemotherapy, radiotherapy and surgery. Targeted approaches and hormonal therapies are also available depending on the subtype, apart from triple-negative

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Abbreviations: BPA, bisphenol A; BPAF, bisphenol AF; BPS, bisphenol S; BPF, bisphenol F; BC, breast cancer; EDCs, endocrine-disrupting chemicals; TME, tumour microenvironment; TEBs, terminal end buds; TDLUs, terminal ductal lobular units; CAFs, cancer-associated fibroblasts; TNBC, triple-negative breast cancer

Key words: breast cancer, endocrine-disrupting chemicals, bisphenols, BPA, BPA analogues, BPAF, BPS, BPF, breast microenvironment

BC (TNBC) which is associated with the poorest prognosis (6). While epithelial cells predominantly drive BC pathogenesis, its progression is widely accepted to be influenced by components of the breast microenvironment, a rich milieu, which includes fibroblasts, adipocytes, and immune cells such as macrophages, mast cells and T-cells (7-10).

Endocrine-disrupting chemicals (EDCs) are environmental substances known for interfering with the normal functioning of the endocrine system (11). These chemicals can mimic, block, or disrupt various processes related to the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body (12). Hence, there is potential to impact cellular function and increase the risk of carcinogenesis. Exposure to EDCs can occur through ingestion, inhalation or dermal contact, for example with contaminated air, water, food, consumer products, or contaminated surfaces (11,13-15). EDCs interfere with and modulate the endocrine system, and can lead to various adverse effects, such as alterations of the hypothalamic-pituitary-adrenal axis and urogenital tract malformations, and may also contribute to the development of BC (16). By disrupting the cellular microenvironment, EDCs may affect cell signalling, communication and the extracellular matrix, contributing to a pro-carcinogenic environment.

Bisphenols are some of the most commonly recognised EDCs (11), with bisphenol A (BPA) being the most well-known. Alternatives to BPA, include bisphenol AF (BPAF), bisphenol S (BPS) and bisphenol F (BPF), which share structural similarities with BPA (17). In response to regulatory measures, use of BPA has been increasingly restricted (11) while alternatives, particularly BPS and BPF, have gained favour as replacements (18). However, despite being postulated as safer substitutes, BPAF, BPS and BPF exhibit comparable structural characteristics and demonstrate similar oestrogenic, androgenic, anti-oestrogenic and anti-androgenic activities both *in vivo* and *in vitro* (19). These properties suggest that these compounds may influence cellular processes in ways that could elevate the risk of cancer development. Therefore, a comprehensive evaluation of BPA and its alternatives is essential to fully assess their potential implications in BC development, and to determine whether these BPA substitutes are safer alternatives.

The present narrative review aimed to provide a comprehensive summary of the available literature to determine the potential role of BPA and its chemical analogues (BPAF, S and F) on the cell types that reside within the breast microenvironment (Fig. 1) and to determine how this may influence BC development.

2. Bisphenols

BPA. The structure of BPA is illustrated in Fig. 2, a synthetic xenoestrogen used in the manufacturing of polycarbonate plastics and epoxy resins (20). BPA has been extensively investigated for its effects on nuclear receptor signalling pathways and has been found to be disruptive (21). For example, high-dose BPA predominantly functions as an oestrogen receptor (ER) antagonist through modulating genomic transcription (22). Conversely, at nanomolar doses, BPA is considered to interfere with biological processes through non-genomic mechanisms facilitated by membrane signalling (23). Materials containing

BPA are various and include plastic containers, tin cans, water bottles, toys, healthcare equipment and up to 2020, thermal paper (including till receipts) (24). Consumer exposure primarily occurs through food coming into contact with BPA-containing materials, such as polycarbonate baby bottles, food containers, and epoxy resin-lined food and beverage cans. The impact of BPA on human health has led to the implementation of various regulatory measures aimed at limiting lifetime exposure. For instance, the European Food Safety Authority (EFSA) has reduced the recommended tolerable daily intake (TDI) of BPA from 4 µg/kg bodyweight/day (set in 2015) to 0.2 ng/kg bodyweight/day (set in 2023) (25), a 20,000-fold decrease. Additionally, the use of BPA in baby products was completely banned in the EU from 2011 onwards (26). In 2024, the EFSA issued a statement for phasing out BPA and its analogues in consumer products (27). By contrast, in the USA, the TDI has not been changed since it was first introduced in the 1980s and still stands at 50 µg/kg bodyweight/day (28). Furthermore, numerous petitions with new evidence indicating the potential adverse effects of BPA have failed to initiate a review or reduction of the current TDI (29).

BPA chemical analogues. The growing public awareness surrounding the potential adverse effects of BPA on human health has placed manufacturers under significant pressure to eliminate their use, resulting in the emergence of 'BPA-free' products. However, many of these contain BPA analogues, including BPAF, BPS and BPF (Fig. 2), whose use currently remains unregulated (30). Despite research efforts into the potential oestrogenic effects of these alternatives, the available literature remains limited. A single systematic review of 32 studies highlighted the significant knowledge gaps on their impact (19). Nonetheless, findings from preclinical studies have shown considerable endocrine-disrupting effects of BPA, BPS and BPF at micromolar values (31,32). Phenotypic and proteomic changes were observed within a human-derived normal breast organoid model exposed to 15 nM BPA, BPS and BPF. This included the disruption of tissue architecture and abnormal branching (33). Another study on human breast cancer cell lines demonstrated that BPAF was a more potent activator of ER α than BPA (34). Moreover, animal studies have shown that BPS and BPF have direct oestrogenic activity; for instance, BPS and BPF can induce uterine growth in rodents (35,36) and disrupt reproduction in zebrafish (37).

3. Bisphenols and the breast microenvironment

Investigations into the potential oestrogenic effects of BPA and its analogues have been extensive in normal and cancerous breast epithelial cells, as reviewed extensively elsewhere (38-40). The present review provides insight into the potential effects of BPA on other cells found within the breast microenvironment, including fibroblasts, adipocytes and immune cells.

Fibroblasts. Fibroblasts are the primary cellular constituents of the breast stroma and undergo activation and proliferation in response to various stimuli, including inflammation, wound repair and malignancy (41,42). In addition, fibroblasts can regulate mammary epithelial cell morphogenesis, including

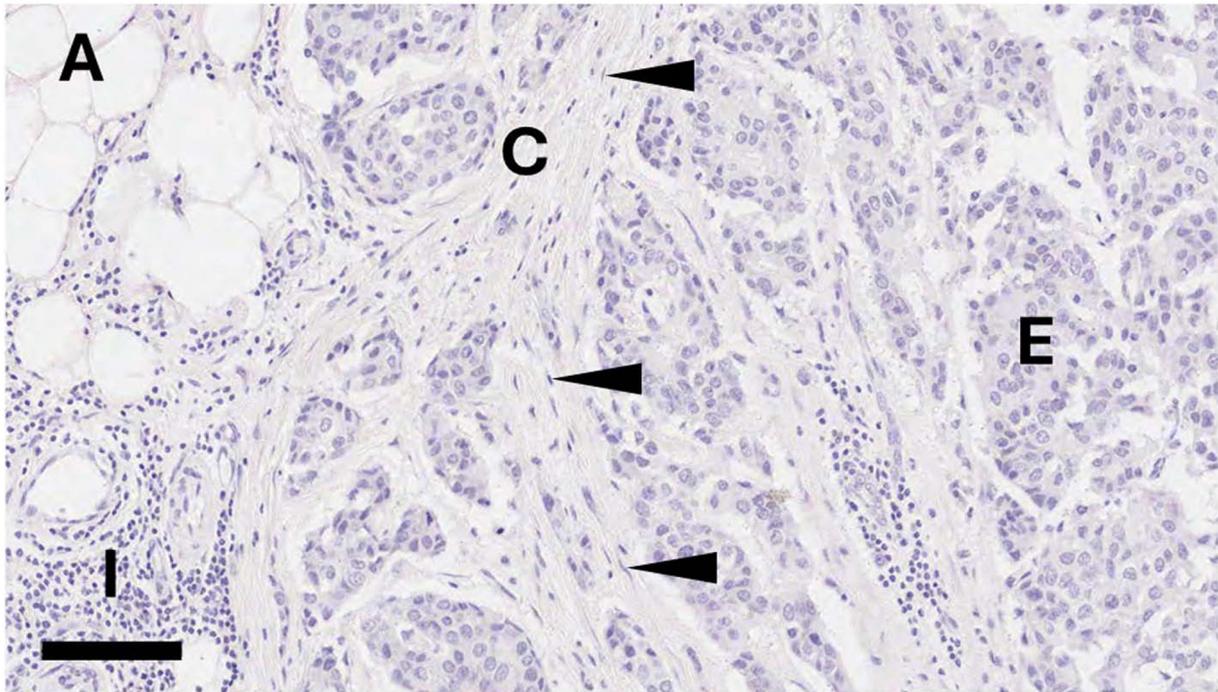


Figure 1. The microenvironment of breast cancer. Haematoxylin- and eosin-stained section of a formalin-fixed paraffin-embedded breast tumour. Cancer epithelial cells (E) reside in a collagen-rich microenvironment (C) alongside adipocytes (A), assorted immune cells (I) and fibroblasts (arrowheads) which collectively comprise the tumour microenvironment. Scale bar, 100 μ m. The tissue image was generated from an anonymised breast tissue sample donated with ethical approval to the Leeds Breast Tissue Bank (15/YH/0025) whose samples now reside in the Breast Cancer Now Biobank (23/EE/0229).

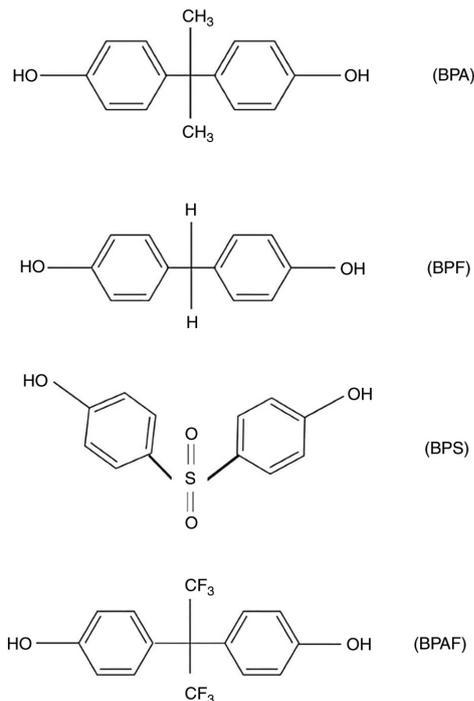


Figure 2. Chemical structure of BPA, BPF and BPAF. The image was created using BioRender.com. BPAF, bisphenol AF; BPS, bisphenol S; BPF, bisphenol F.

expansion, differentiation, ductal elongation and invasion into adipose tissue (43). The development of fibrous connective tissue, typically in response to injury or damage, results in

fibrosis, a process known to be associated with an increased risk of malignancy (44). Fibroblasts and myofibroblasts undergo genetic alterations, predisposing them to transform into cancer-associated fibroblasts (CAFs), which play a pivotal role in tumour development, stromal remodelling, and intercellular communication pathways (45). Collectively, these actions create a tumour-supportive microenvironment and contribute to resistance to anticancer therapies (46).

Previous studies on the immune regulation of mammary fibroblasts have highlighted the role of immune cells in regulating fibroblast function within the mammary gland, which impacts mammographic density, a known risk factor for BC development (47-50). Mammographic density is dependent on the proportions of epithelial and fibrous stromal tissues. Increased mammographic density is analogous with a higher content of fibrous tissue within the stroma and is associated with a 4-6-fold increased risk of developing BC (50). Studies have shown that exposure to BPA promotes collagen production by cardiac fibroblasts via the ERK1/2 pathway (51), and is associated with an elevated mammographic density (52) and increased mammary gland rigidity, a property which is known to enhance proliferation and tumour progression (53). Fibroblast-driven paracrine signalling and extracellular matrix remodelling, as mediated by the EGFR pathway; this further influences epithelial morphogenesis and may play a role in tumour initiation (54).

A previous study investigating the effects of BPA on co-cultures of CAFs and breast cancer cells, demonstrated that BPA mediated CAF proliferation and SkBr3 migration through the activation of the G-protein coupled ER pathway (55). Primary mammary fibroblasts from mouse mammary glands

exposed to BPA exhibit the differential expression of genes commonly associated with an increased risk of developing BC (56).

BPA exposure significantly alters the gene expression profiles of mesenchymal cells, including fibroblasts, derived from murine mammary glands (57), disrupting their function and behaviour by influencing pathways associated with extracellular matrix production. These disruptions could potentially alter fibroblast-epithelial interactions, affecting mammary gland development and potentially predisposing the tissue to developing malignancy.

There are a limited number of studies investigating the effects of BPS and BPF on fibroblasts. Potential cytotoxic effects of these compounds on mammalian fibroblasts, at 50–500 mM doses has been reported; however, the use of such high concentrations is questionable compared to real-world exposure levels (58). In MRC5 human lung fibroblasts exposed to up to 100 μ M BPA, no effects were observed on proliferation, cell cycle progression or apoptosis (59).

Adipocytes. Adipocytes are abundant in the breast tumour microenvironment (TME). White adipocytes are a major component and primarily store energy as triacylglycerol, releasing this as fatty acids and glycerol under high metabolic demand (60). Breast adipocytes are increasingly associated with BC development and progression (61). In a previous study using mice exposed to oral BPA (5, 50, 500 and 5,000 μ g/kg/day) alongside normal chow, bodyweight and adiposity increased, indicating the potential interaction of BPA with diet (62). Furthermore, BPA increased circulating inflammatory factors leptin and tumour necrosis factor (TNF)- α in lean female, but not male mice (62). At an endocrine level, obesity poses a significant risk factor for ER⁺ BC due to the aromatisation of androgens to oestrogens in adipocytes, which elevates the overall oestrogen levels (63). This also extends to BC in males, where research has demonstrated that the increasing number of males receiving a BC diagnosis parallels with an increase in obesity (64).

Some endocrine disruptors can modify inflammatory responses in adipocytes (62). Cancer-associated adipocytes (CAAs) are adipocytes located close to the tumour leading edge and are characterised by loss of lipid content, loss of mature adipocyte markers, such as peroxisome proliferator-activated receptor γ (PPAR γ), and an increase in adipokines, primarily leptin and resistin, which can promote BC development (65–67). Additionally, CAAs display an increased secretion of inflammatory mediators, including interleukin (IL)-1 β , IL-6 (68), vascular endothelial growth factor (VEGF) and TNF- α , potentially in response to cancer cells (69). Moreover, CAAs release adipokines that promote cancer cell migration, such as IL-6 and monocyte chemoattractant protein-1 (MCP-1) (70), at higher levels compared to non-cancer adipocytes (70). BPA increases the expression of these adipokines to help facilitate their role in breast carcinogenesis. For example, in a previous study, when mature human adipocytes were treated with 0.1 nM BPA, the G protein-coupled oestrogen receptor pathway was activated, leading to the release of IL-6, IL-8 and MCP1 α (23). Both IL-6 and MCP-1 α can promote cancer cell proliferation and migration, and IL-8 enhances the invasiveness and angiogenesis of BC cells, particularly

ER⁺ subtypes (68,71). The implication of these findings is that BPA may cause adipocytes in the breast microenvironment to release pro-inflammatory cytokines, potentially accelerating tumour development and growth.

BPA has also been implicated in altering hormone levels in adipose tissue by modulating the activity of key regulators, such as lipoprotein lipase and aromatase (72,73). Although limited, studies on the effects of BPA on breast adipocytes have shown that nanomolar concentrations of BPA do not stimulate the proliferation of adipocytes in human subcutaneous adipose tissue (74). However, several studies have demonstrated that BPA accelerates adipocyte differentiation into mature cells *in vitro* (75–80). For instance, murine 3T3-L1 cells and adipocyte stem cells undergo accelerated differentiation into mature adipocytes upon exposure to low concentrations of BPA (10–80 μ M) (75–80). Mature adipocytes are crucial for secreting adipokines, such as adiponectin, which have anti-inflammatory and antioxidative properties, and can inhibit cell proliferation and angiogenesis (81). In addition, adipokines promoted apoptosis in diabetes (82). If these effects are mirrored in BC, this may provide potential protective effects. Conversely, exposure to 0.1 and 1 nM of BPA has been shown to decrease adiponectin release from human breast adipose tissue (83). In metabolic disorders, adiponectin functions as a protective factor, promoting insulin sensitivity and exhibiting anti-inflammatory and anti-tumorigenic properties (84).

Both preadipocytes and mature adipocytes significantly influence mammary gland development, with preadipocytes promoting epithelial branching and elongation, as demonstrated in mouse models (85). *In vivo*, murine studies have indicated that prolonged exposure to both 1 and 10 μ g/ml BPA, classified as low and high concentrations, respectively, influences obesity and hyperlipidaemia development during perinatal and postnatal periods (86). In another study, the *in utero* exposure of mice to BPA at 250 ng/kg/day increased the expression of PPAR γ and other adipogenesis-related genes (57). In addition, BPA exposure has been shown to increase the concentration of mature adipocytes, negatively influencing lumen formation in the foetal mammary gland epithelium (57,87). Additionally, oestradiol sensitivity is increased (88), potentially elevating risk of carcinogenesis. Collectively, these results suggest that, at least in mouse models, *in utero* BPA exposure may be a critical window for abnormal changes in epithelial, stromal and adipose cells, potentially enhancing carcinogenic potential in adulthood.

BPA alternatives, BPAF, BPF and BPS have been shown to alter leptin hormone levels and increase lipid accumulation in the murine 3T3L1 cell line (89). Leptin is secreted by adipocytes and plays a critical role in energy balance and appetite regulation. It also exerts pro-inflammatory effects and may affect cancer progression (90). In a previous study, in 3T3-L1 cells, exposure to 32 μ M BPS and BPF increased the number of differentiated adipocytes and their ability to store more lipids compared to BPA, indicating a higher obesogenic potential and endocrine toxicity (91). Furthermore, in adult mice, doses of both 10 nM and 1 μ M BPS resulted in the upregulation of the expression of PPAR γ and perilipin 1, both involved in preadipocyte differentiation, much earlier in the differentiation process than BPA and BPF. Hence, BPS exposure may contribute to increased adiposity and an increased risk of developing BC.

However, the effects of BPF on adiposity are reduced (92). These contrasting findings suggest uncertainty over the potential influence of BPS and BPF on the risk of developing BC. On the other hand, a previous study demonstrated that BPAF treatment (5 μ M) increased lipid accumulation and sensitivity to inflammatory cytokines, including interferon- γ , in differentiating adipocytes (93). This increased sensitivity resulted in a reduction in mitochondrial and cellular respiratory capacity in adipocytes through the suppression of UCPI by interferon- γ , which may also influence BC progression (93). Collectively, these findings demonstrate the potential impact of BPA and its analogues on adipocyte function and the putative link of bisphenols in increasing breast carcinogenesis.

Immune cells. Different immune cell populations often infiltrate breast cancers. This varies between different BC subtypes. For example, TNBC often has high numbers of tumour-infiltrating lymphocytes, which is associated with an improved survival (94). Several studies have identified the importance of lymphoid and myeloid cells, which are primarily located within the epithelium of breast lobules, in breast carcinogenesis, progression and treatment (95-97).

Lymphoid cells. Lymphoid cells, including lymphocytes, such as T-cells, B-cells and natural killer (NK) cells are key components of the immune system. In a previous study, human T-cells exposed to nanomolar concentrations of BPA exhibited a reduced telomerase activity in CD8⁺ but not CD4⁺ T-cells, accompanied by telomere shortening and human telomerase reverse transcriptase suppression, suggesting adverse effects of BPA on T-cell responses (98). In another study, a 30-day chronic exposure of the human BC cell lines, MCF-7, SkBr3 and MDA-MB-231 to physiologically relevant BPA concentrations (10 nM) upregulated the expression of genes associated with NK cell and T-cell activation, suggesting the potential of BPA to modulate immune function (99). Notably, each cell line exhibited distinct gene expression changes related to immune responses. In MCF-7 cells, *IL-19* expression was upregulated, while in SkBr3 cells, the upregulation of *CXCL5* was linked to BC progression (99). Further research has highlighted an abundance of NK cells in HER2⁺ and TNBC subtypes, with their presence being associated with increased lymphocyte infiltration and a higher grade (100), suggesting that NK cell activation is associated with more advanced BC. These findings underscore the complex immune-related gene expression alterations induced by BPA, implicating its potential role in BC progression through immune modulation.

Myeloid cells. Myeloid cells, including monocytes, macrophages and granulocytes contribute to TMEs by modulating immune responses, promoting inflammation, and supporting tumour growth and metastasis. The immune subtyping of myeloid cells in murine breast cancer models and in clinical datasets has identified neutrophil- and macrophage-enriched subtypes (101).

Neutrophils circulate in the bone marrow and peripheral blood, recognising pathogens through host protein interaction, aiding in phagocytosis, pathogen clearance and tissue regeneration. To the best of our knowledge, no studies to date have examined the effect of BPA on neutrophils in BC. However, an examination of the effects of BPA on human T-cells *in vitro*

indicated increased reactive oxygen species (ROS) production, which is associated with breast carcinogenesis (102).

Macrophages are classified into two main types: M1, which is associated with anti-tumour immunity, and M2, which is linked to pro-tumorigenic properties (103). Evidence from animal models suggests that BPA may alter tumour-associated macrophage (TAM) phenotypes (104). Another study assessed the effects of BPA on macrophage polarisation, demonstrating a significant increase in M2 markers (Arg-1 and CD206) and a reduction in TAMs with M1 markers in ductal carcinomas exposed to 10 nM BPA, which is typically considered an environmentally relevant concentration (105).

BPA alternatives may also influence immune cell activation and differentiation (106). While there are no BC studies, at least to the best of our knowledge, studies using zebrafish and carp have demonstrated that BPS and BPF exert immunotoxic effects by modulating immunoregulatory genes in a concentration-dependent manner during early development. Furthermore, exposure to BPF increases the levels of immunomodulating chemokines and cytokines and is associated with elevated ROS levels, oxidative stress and the upregulation of inflammatory cytokine genes (107,108). The effects of BPA on human myeloid cells in BC macrophages have yet to be determined.

4. Discussion and future directions

The present narrative review demonstrates that BPA and its chemical analogues; BPAF, BPS and BPF, exert diverse effects on the breast microenvironment. Some of these effects may promote BC development, for example, through structural and epigenetic changes to epithelial cells, the disruption of fibroblast functions and stromal modifications, altered adipocyte differentiation, and influences on lymphoid immune activity. Previous studies on the effects of BPA on the female breast microenvironment have mainly focused on BPA, overlooking its analogues and the critical role of non-epithelial cells in the breast milieu. To the best of our knowledge, the present review is the first to systematically compare the differential effects of BPA and its analogues on adipocytes, providing new insight into how these compounds may alter breast tissue composition and function. In addition, the present review also highlights safety concerns regarding BPA analogues and the urgent need for regulatory guidelines.

As demonstrated herein, one of the most critical issues surrounding research on BPA is the reliance on animal models and *in vitro* cell lines, which take a reductionist approach and fail to fully capture the complexity of the breast microenvironment. While these models have provided valuable insight, their translational relevance remains limited. For instance, current animal model limitations include murine mammary tissue, which contains terminal end buds (TEBs) vs. terminal ductal lobular units (TDLUs) found in humans. TDLUs are specialised structures containing collagen, hyaluronan and other matrix proteins, and give rise to primary sites where ductal carcinomas can occur (109). By contrast, mouse TEBs lack such specialised stroma, primarily comprising adipose tissue with few fibroblasts (109). Furthermore, research has highlighted that murine mammary cytokines may not functionally match human receptor interactions, limiting

the translational relevance of these models (110). To address these shortcomings, recent advancements have introduced humanised models including organoid cultures, 3D co-culture systems and clinical sample analyses, which better replicate the breast microenvironment by preserving multicellular contacts and immune interactions. Incorporating these models could improve the clinical applicability of BPA research in future. Additionally, the majority of available studies have examined single compounds and have overlooked the combined effects of multiple chemicals or 'cocktail effects', which may lead to underestimating the real-world risks. Future research is thus warranted to incorporate experimental designs that consider mixed bisphenol exposures to provide a closer representation of the environmental risks. Moreover, the heavy reliance on cell lines does not address the potential role of BPA in initiating breast carcinogenesis.

To overcome these limitations, future studies are required to focus on the effects of BPA and its analogues on all cells within the breast microenvironment, particularly in the context of cancer-stromal interactions, using multicellular 3D models (111). A critical aspect of BPA-induced breast carcinogenesis may lie in its ability to remodel the TME. CAFs, key components of the TME, play an essential role in metabolic symbiosis with tumour cells and contribute to immune escape mechanisms by modulating cytokine signalling. Bisphenols may enhance CAF activation, leading to extracellular matrix remodelling, increased tumour invasiveness and altered immune responses. Thus, further studies using tumour niche models and stroma-epithelium interaction assays are required to elucidate the mechanisms through which BPA and its analogues promote breast cancer progression. Studies should also aim to use more reflective models and novel technological advances to better understand BPA and its alternatives, and their impact on the TME, as well as to determine safe cut-off levels to guide regulatory recommendations to prevent toxic harm. The use of organoids derived from cancerous and non-cancerous human breast tissue is recommended (112), that can recapitulate their primary tissue both phenotypically and molecularly (113). Although definitive evidence is currently lacking, an observational study of male BC across various regions of Scotland found higher incidence rates in areas with significant agricultural activity, where the use of pesticides and EDCs may be more prevalent (114). As such, tissue collection efforts should include both males and females (114). Multi-cellular 3D models of cell lines (115), co-culture approaches (116) and the use of novel bioprinting techniques (117), would enable a more insightful representation of microenvironmental complexity. In addition, the use of breast-on-a-chip models would enable microfluidic techniques to create controlled, miniaturised environments for studying dynamic tissue interactions with greater precision (118). To permit the comprehensive mapping of cellular interactions and molecular changes within breast tissue exposed to BPA and its analogues, the use of emerging spatial multi-omics technologies should also be utilised (119). Drawing insights from the Human Breast Cell Atlas (120), a comprehensive map of cell types found within the normal human breast, may inform these studies and enhance our understanding of the tissue-specific impacts of bisphenols. Lastly, a thorough investigation into both the short- and long-term effects of

BPA on various mammary cells, alongside sensitivity testing across low, medium, and high BPA exposure levels, is crucial for making any meaningful study comparisons and guiding regulatory decisions on safe exposure limits.

Another observation was the wide variation in doses of bisphenols used experimentally, ranging from 500 mM (58) to 10 nM (105). Optimum concentrations should be defined to allow their biological effects to be defined more rigorously. It is also recognised that these chemicals are pervasive in the environment which may be confounding, although this is difficult to control.

Finally, from a regulatory and public health perspective, there is a lack of consensus regarding the threshold for BPA exposure, making it challenging to define what constitutes 'safe' exposure levels. This inconsistency is particularly evident when comparing international guidelines; for instance, the US TDI currently stands at 50 $\mu\text{g}/\text{kg}$ body weight/day, which is 250,000-fold higher than the European TDI of 0.2 ng/kg body-weight/day (28,121). In the UK, recent estimates indicate that average daily exposure to BPA is ~ 2.5 ng/kg body weight/day, depending on dietary habits and environmental factors (122); however, precise numbers are difficult to assess. Moreover, the term 'chronic BPA exposure' is inconsistently defined among studies, impeding cross-study comparability. Consequently, the potential impact of bioaccumulation on breast carcinogenesis remains largely unexplored. It is also important to highlight that BPAF, BPS and BPF currently lack regulatory oversight, a concern underscored by the findings presented herein, as these unregulated compounds may be driving the same pheno- and genotypic changes as found in BPA.

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Availability of data and materials

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Authors' contributions

ST was involved in the writing, reviewing and editing of the manuscript and in the writing of the original draft, as well as in visualization (figure preparation) and project administration. KK was involved in the writing, reviewing and editing of the manuscript. KP and AD were involved in the writing, reviewing and editing of the manuscript, as well as in data curation (assessing all the relevant research articles for inclusion in the review). DPMC was involved in the writing, reviewing and editing of the manuscript, in visualization and study supervision, as well as in project administration, methodology, investigation, formal analysis, data curation and in the conceptualisation of the study. VS was involved in the writing, reviewing and editing of the manuscript, as well as

in visualization, study supervision and project administration, resources (funding for the study and the tissue image), and in the conceptualisation of the study.

Ethics approval and consent to participate

The tissue image included in Fig. 1 was generated from an anonymised breast tissue sample donated with ethical approval from the Leeds Breast Tissue Bank (REC 15/YH/0025), whose samples now reside in the Breast Cancer Now Biobank (REC 23/EE/0229). As the sample was provided with full anonymisation, the donor cannot be identified meaning that written informed patient consent was not required.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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